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The Editorial

Is “re-calibration” of standard cardiovascular disease (CVD) risk algorithms the panacea to improved CVD risk prediction and prevention?

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Cardiovascular disease (CVD) remains the leading cause of death globally and its prevention is still suboptimal. Cardiovascular risk assessment is a fundamental component of CVD prevention – the common approach involves identifying individuals at high CVD risk and targeting them for lifestyle and pharmacological interventions. Guidelines by the American College of Cardiology/American Heart Association (ACC/AHA) task force[1] and the European Society of Cardiology (ESC)[2] are the major CVD prevention guidelines that are influencing clinical practice. These guideline bodies recommend the Pooled Cohort equations and the Systematic Coronary Risk Evaluation (SCORE)[3, 4] algorithm respectively for 10-year CVD risk estimation. Other well-known CVD risk algorithms include the Framingham Risk Score (FRS)[5] and the Reynolds Risk Score (RRS).[6, 7] The performance of a risk prediction score is assessed using measures which include calibration and discrimination.[8] Calibration as measured by the goodness-of-fit statistic, is the ability to correctly estimate the risk of a future event. Discrimination is the ability of the risk score to separate individuals at higher risk from those at lower risk and it is assessed using the area under the receiver-operating characteristic (ROC) curve or C statistic (Harrell's C-index[9]).[8]

The Pooled Cohort equations employed by ACC/AHA guidelines are based on any atherosclerotic CVD (ASCVD) events;[1] whereas SCORE is based on fatal CVD outcomes.[3, 4] In addition, different risk thresholds are recommended for statin treatment initiation in primary CVD prevention. The ACC/AHA has lowered the threshold for statin initiation to a 7.5% 10-year risk of ASCVD;[1] in contrast, the ESC has preserved the 5% 10-year risk for fatal ASCVD estimated by SCORE.[10] Reports from previous studies have indicated varying performances of these scores in different populations.[11-13] The ACC/AHA risk calculator has been suggested to overestimate CVD risk.[11] The SCORE model with a restricted age range (40-65 years) has focused on fatal ASCVD thereby disregarding nonfatal events.[3] Due to the varying risk for fatal ASCVD across Europe, two standard versions of SCORE models were recommended by the 2003 ESC guidelines[10] – low and high risk SCORE versions for low and high CVD mortality countries respectively. Given the declining rates of fatal ASCVD across most of Europe, it appears many European countries are using miscalibrated SCORE models.[14] Therefore, there have been calls to re-calibrate SCORE to target populations, as risk models perform best when used in the population from which it was developed.[14] Risk scores need to be well calibrated to the target population when decisions regarding treatment initiation are based on absolute risk. To generate more accurate CVD risk prediction for a particular population, risk models need to be re-calibrated.
There is paucity of large-scale studies that have provided head-to-head comparisons of standard risk prediction algorithms.

To address how four widely-used risk prediction algorithms (PCE, SCORE, FRS, and RRS) differ in their predictive accuracy and clinical performance, Di Angelantonio and colleagues compared original and re-calibrated versions of these algorithms across multiple settings in an elegant analysis.[15] The authors employed data on over 350,000 people (aged 40-79 years) without known CVD at baseline using comprehensive statistical analyses on risk scores re-calibration based on 86 prospective cohorts. For each participant, they implemented original versions of FRS, SCORE, PCE and RRS to calculate the predicted 10-year CVD risk. These scores were then re-calibrated using the risk factor profile and CVD incidence of the target populations.

The four evaluated risk scores vary in their risk factors and CVD endpoints (**Table**). The use of uniform criteria for outcomes needs serious consideration when evaluating the value of risk scores. CHD outcomes manifest in various ways such as sudden cardiac death, acute coronary syndromes, myocardial infarction (MI), and diagnosed using different non-invasive exercise testing and imaging techniques, such as coronary computed tomography, perfusion imaging and coronary angiography, which may have effects on numbers diagnosed patients with CHD over time. The Emerging Risk Factor Collaboration (ERFC) study used definitions of nonfatal MI based on the World Health Organization criteria and of nonfatal stroke based on clinical and brain imaging features.[17] In coding fatal outcomes, all contributing studies classified deaths according to the International Classification of Diseases. To facilitate head-to-head comparisons, the study group recalibrated SCORE and RRS to the common CVD outcome employed by FRS and PCE.

The main finding was that the performance of the original four risk algorithms varied substantially, predominantly due to differing extent of calibration.[15] However, after re-calibration, their performance was equalised. The authors found only minor differences among the algorithms in relation to risk discrimination based on the Harrell's C-index, which is a measure of predictive accuracy that is not influenced by the extent of model calibration. Di Angelantonio and colleagues concluded that targeting of CVD preventive action to clinical practice would improve considerably due to higher accuracy of individual risk predictions.[15] One potential implication is that primary prevention guidelines should shift away from debates about the relative merits of certain risk algorithms and instead, achieve consensus about the need for more widespread use of any re-calibrated algorithm.

To further evaluate the clinical usefulness of these available risk algorithms in the decision to initiate therapies such as lipid lowering drugs, the authors were able to estimate the number of individuals who would benefit from statin treatment. To conduct this analysis, certain

assumptions were made: risk assessment for a population of aged ≥40 years without CVD and not already taking statins or meeting recommendations for statin treatment; including the same age structure of a standard population of the United States; age- and sex specific incidence rates for CVD events as in the current study; and statin use allocation according to the predicted 10-year CVD risk threshold by ACC/AHA guideline for first-onset fatal and non-fatal CVD events (i.e., ≥7.5%), or by the ESC Guidelines for fatal CVD (i.e., ≥5%), with risk reduction of 20% with statin treatment in primary prevention. Based on re-calibration, it seemed that the proportion of individuals classified as high-risk reduced from 40% to 23%, and the number of individuals needed to initiate statin therapy to prevent one event reduced from 44-51 to around 38. This indicates an average improvement that could be achieved by re-calibration across a set of different populations.[15]

The illustrations of the paper (e.g. Figure 4) clearly demonstrate the number of people classified as high-risk groups when using the specific risk scores and the substantial change after re-calibration calculations.[15] It is not encouraging for clinicians if they are unable to rely on CVD scores in the decision to initiate drug therapy, of course, in addition to prescribing well documented life-style interventions such as physical exercise and healthy diet. To facilitate better clinical decision making, risk predictions need to be improved and appropriate population-wide thresholds should be set. Without accurate individual risk predictions, clinicians should not readily prescribe medications that could potentially be harmful. This relates especially for primary prevention as compared to drug initiation in secondary prevention populations in high-risk groups i.e. after the first non-fatal CVD event among patients with underlying atherosclerosis with evidence of the effects of drugs. As the number needed to treat is quite high in primary prevention populations, it may not be acceptable to initiate therapy that has the potential to cause harm. Regarding assessments of medication use; though a limitation, the authors clearly acknowledged that it was not possible to formally incorporate the impact of the potential hazards of the use of drugs in all included population studies. Second, information on medication use (lipid lowering, antihypertensive or antithrombotic drugs), including widely used invasive interventions such as percutaneous coronary intervention and coronary artery bypass surgery with active cardiovascular rehabilitation, which may have influenced long-term estimates of the observed CVD risk, could not be taken into account.

Prevention with treatment of common risk factors, such as the North Karelia Project in Finland, has been a successful story in cardiology in many Western countries. Effective prevention has moved the age of first evidence of CHD from the younger to the elderly

populace; meaning that more people are capable of continuing their active working lives independently of healthcare systems for longer periods without limitations due to CVDs. On the other hand, the form of CHD may have changed in recent times, patients being treated in the cardiology clinic, are older with co-morbidities compared to decades ago.

This study's main message on the importance of recalibration of risk scores is timely and relevant for advanced CVD prevention. The authors reported findings on the extent of CVD risk prediction improvement using re-calibration. We appreciate and applaud their efforts on pooling prospective studies on CVD risk factors together which extend further evidence on the clinical usefulness of risk scores. The study findings provide robust evidence on the implementation of risk scores helping to tailor therapy in modern CVD treatment; it is highly unlikely there is corresponding data from randomised studies which suggest the implementation of CVD risk assessment can translate into CVD prevention strategies using life-style interventions and drugs. Indeed, these study findings suggest that the use of well re-calibrated risk algorithms in clinical practice could improve targeted CVD prevention on a global scale.

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Table. Cardiovascular risk scores, their risk factors and outcomes in original studies

Score	Included risk factors	Baseline age (range)	Origin	Baseline data collected (year (s))	Main outcome
SCORE	Age, smoking status, total cholesterol, HDL cholesterol systolic BP	40-65	Europe	1967-1991	Fatal non-CHD CVD; fatal CHD
PCE	Age, smoking status, total cholesterol, HDL-cholesterol, systolic BP, diabetes status	40-79	USA	1987-1989; 1990-1992; 1993-1995 / 1989-1999 / 1985-1986 / 1968-1971; 1971-1975; 1984-1987	Non-fatal and fatal CHD or stroke
FRS	Age, smoking status, total cholesterol, HDL-cholesterol, systolic BP, diabetes status	30-74	USA	1968-1971; 1971-1975; 1984-1987	Fatal and non-fatal coronary and stroke events
RRS	Age, smoking status, total cholesterol, HDL-cholesterol, systolic BP, hsCRP, HbA1c (if diabetic), parental history of MI<60 years	Women: ≥ 45 Men: ≥ 50	USA	Women: 1992 Men: 1995	MI, ishemic stroke, coronary revascularization or CVD death

BP = blood pressure; CHD = coronary heart disease; CVD = cardiovascular disease; FRS= Framingham Risk Score; HDL = high density lipoprotein; hsCRP = high sensitivity C-reactive protein; MI = myocardial infarction; PCE = Pooled Cohort Equations; RRS= Reynolds Risk Score; SCORE= Systematic Coronary Risk Evaluation